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Synthesis of Tervalent Phosphorus Esters in Biphasic System Using Potassium Phosphate as Unique Solid Base

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ABSTRACT: *The synthesis of tervalent phosphorus esters continues to be a significant area of interest, much of it again directed toward the synthesis of phosphite ligands for metal-catalyzed reactions. Typically, they were obtained through esterification of the corresponding phosphorus chlorides with the appropriate alcohols in the presence of an amine. In this paper, we present a new method for the synthesis of tervalent phosphorus esters, not yet mentioned in the literature, when potassium phosphate, as a unique base, is used in liquid–solid system. Symmetrical and unsymmetrical phosphites were obtained with good yields (65%–80%) using this method. The compounds were characterized by* ^{31}*P NMR spectroscopy.* Heteroatom Chem 19:360–364, 2008; DOI 10.1002/hc.20438

INTRODUCTION

Organophosphorus compounds have a wide range of applications in the areas of industrial, agricultural, and medicinal chemistry owing to their biological and chemo-physical properties as well as their utility as synthetic intermediates. Many texts on organophosphorus chemistry have been published ranging from in-depth studies of the subject as a whole to more general texts that would serve as a general introduction to the field [1,2].

Besides phosphines and tervalent phosphorus amides, all three classes of tervalent phosphorus acid esters (phosphinites, phosphonites, and phosphite) are of great interest [3].

In recent years, the synthesis of phosphinites has been centered on obtaining new ligands for use in enantioselective homogeneous catalyst systems, in which the phosphinite donor either replaces or complements conventional organophosphino compounds. Among other simple nonchiral systems, aminoalkylbis(phosphinite) [4], "pincer"-diphosphinites (which form the cyclometallated palladium complexes on treatment with palladium trifluoroacetate) [5], and monophosphinites (which also undergo orthometallation with palladium(II) complexes) [6] are described in the literature. Monodentate phosphinite ligands are used in palladium-catalyzed Suzuki reactions [7]. An original series of P-chirogenic aminophosphane-phosphinite (AMPP) ligands has been synthesized from (+)- or (−)-ephedrine. The AMPP ligands were used in the form

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of rhodium complexes for the catalyzed hydrogenation of α-acetamidocinnamate [8].

Currently, there is less interest in phosphonites, and their synthesis is often discussed to be related to phosphite esters or phosphines [9,10].

A typical example is a group of tridentate N,P,N-ligands containing a phosphonite bridge between two chiral oxazolines [11], and a series of enantiopure *C*1-symmetric phosphino-phosphonites with *o*-phenylene backbones, obtained by the reactions of the *o*-phosphinoaryl-diaminophosphine with chiral alcohols. Also BINOL-derived diphosphonite having an achiral backbone based on diphenyl ether is used as a ligand for the enantioselective Ru-catalyzed hydrogenation of β-keto esters [12].

Phosphite esters continue to be a significant area of interest, much of it again directed toward the synthesis of phosphite that is useful for applications in metal-catalyzed reactions. The effectively achiral, conformationally flexible, biphenylylphosphorochloridites have been converted into a series of diastereoisomeric phosphites on treatment with a range of chiral alcohols, in the presence of triethylamine [13,14]. A new family of readily available modular phosphite, phosphoramidite, and diamidophosphite ligands with P*-stereocenters has been synthesized. Using these novel ligands, high yield was achieved in the Pd-catalyzed asymmetric allylic amination [15].

Novel monodentate phosphites, containing ortho- and meta-closododecarboranyl groups, have been synthesized and applied in the asymmetric Rh-catalyzed hydrogenation of dimethyl itaconate [16]. Using chiral binaphtholic phosphite, a highly enantioselective rhodium-catalyzed addition of arylboronic acids to *N*-tosylarylimines is described [17]. Also stannyl complexes of ruthenium and osmium stabilized by polypyridine and phosphite ligands were prepared [18].

Even though these classes of tervalent phosphorus esters were synthesized earlier, the interest is constantly increasing due to their use, especially in Michaelis–Arbuzov [19–22], Perkow [23–25], and Kabachnik–Fields reactions [26].

The usual method for obtaining tervalent phosphorus derivatives is esterification of appropriate phosphorus chloride with an alcohol or phenol. Even though the literature on tervalent phosphorus derivatives is large, the variety of synthetic approaches is limited to their use as an organic base.

In this paper, we present a new method for the synthesis of tervalent phosphorus esters, namely phosphites, not yet mentioned in the literature, when potassium phosphate is used as a unique base.

The use of potassium phosphate as a high-performance base has attracted some interest in recent years. It was shown [27] that potassium phosphate is a selective solid base in phase-transfer-catalyzed alkylation reactions, exceeding the performance of common bases such as hydroxides, carbonates, fluorides, and oxides. Tetra-*O*-acetylglycosides were obtained under solid–liquid phase transfer catalysis using anhydrous potassium phosphates [28]. Potassium phosphate was used in Suzuki–Miyuara coupling reactions of benzyl phosphates with arylboronic acids [29], for homocoupling of naphthyl triflates [30], for synthesis of unsymmetrical substituted *meso*-phenylporphyrins [31], or for total synthesis of altenuene and isoaltenuene [32], This base was used in arylation of allylic acetates by controlled microwave heating [33]. Potassium phosphate was used in the microwave-mediated solvent-free Rap–Stormer reaction for synthesis of benzofurans [34] and for oxidative coupling of thiols to disulfide [35].

RESULTS AND DISCUSSION

Tervalent phosphorus derivatives may be deemed to come directly or indirectly from tervalent phosphorus chloride derivatives and an alcohol or phenol [36]. Two aspects of alcohol-phosphorus halide system were known almost independently since about 1904; the first one is related to the preparation of alkyl halides, and the other one is related to how to obtain different esters.

The preparation of simple or mixed phosphites is illustrated in Scheme 1 and is applicable to both alkyl and aryl systems.

In all these reactions, an organic base is involved (i.e., triethyl amine, pyridine, and so on), which forms a salt with hydrogen chloride. However, without the base the reaction leads to the formation of a dialkylphophosphite and an alkyl chloride (Scheme 2).

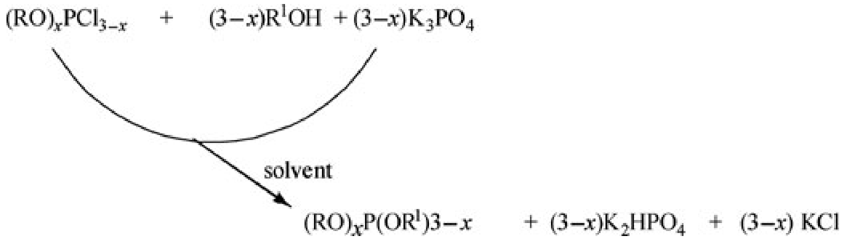
Under certain conditions, the reaction may lead to only the alkyl chloride and phosphorous acid. The use of the organic base has many disadvantages such as

$$PCl_3 + 3\,C_2H_5OH + 3\ \text{base(organic)} \longrightarrow (C_2H_5O)_3P + 3\ \text{baseHCl}$$

SCHEME 1 Synthesis of triethylphosphite [36].

$$PCl_3 + 3\,C_2H_5OH \longrightarrow (C_2H_5O)_2P(O)H + C_2H_5Cl + 2\,HCl$$

SCHEME 2 Synthesis of diethylphosphite [36].



SCHEME 3 The new proposed method for the preparation of tervalent phosphorus esters using a phase-transfer catalyst (reaction time: 3 h; reaction temperature: 20°C; base: potassium phosphate; phase transfer catalyst: tetrahexylammonium chloride).

- the reaction is exothermic, and the mixture requires intense cooling;
- the use of an equimolecular amount of amine ensures an acceptable yield of phosphite;
- the separation of ammonium salt is laborious and sometimes ineffective;
- all reaction products are inevitable unpurified with amine and salts.

These disadvantages can be overcome by using a process in which potassium phosphate is used as a unique base and the phase-transfer catalysis as a technique (Scheme 3).

The investigation was started to find optimal conditions for the synthesis of tervalent phosphorus derivatives by using this technique. Trimethylphosphite was used as a test compound in comparison with a commercially available standard (Aldrich, Bucharest, Romania). The reaction between methanol and phosphorus trichloride was monitored by HPLC (Figs. 1 and 2). The retention times were the same (2.6 min) for the reaction product and the standard.

In phase-transfer catalysis reactions, many parameters are involved that influence the development of the process such as stirring speed, type of catalyst, reaction time, and speed of mass transfer. One of the parameter that we evaluated was the stirring speed since it has a relevant influence on the mass transfer processes and on the reaction rate.

The reaction rate increases when the area of the surface contact between the two phases is increased. The experiments were performed in a 50-mL flask and using a Teflon magnetic stirring bar with a semicircular shape.

The best results were obtained at 600–650 rpm. Furthermore, the influence of the reaction time on the yield was studied. The yields are not influenced significantly by the reaction time because side reactions are reduced to the minimum. The reaction time was 3 h for all the experiments. The influence of the phase-transfer catalyst was also studied.

The best results were obtained with tetrahexylammonium chloride. The obtained results are summarized in Table 1.

The yields are good for all synthesized compounds. As it is known, tervalent phosphorus derivatives are sensitive to hydrolysis. The use of other solid bases, such as potassium carbonate or sodium

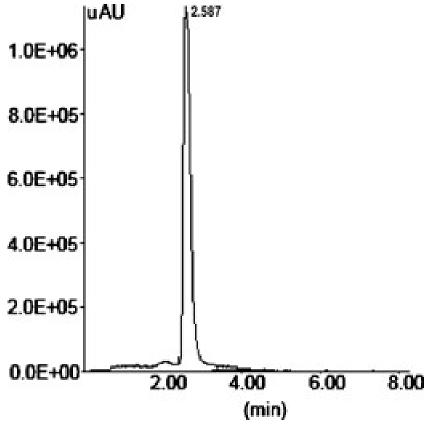


FIGURE 1 HPLC chromatogram for trimethylphosphite standard.

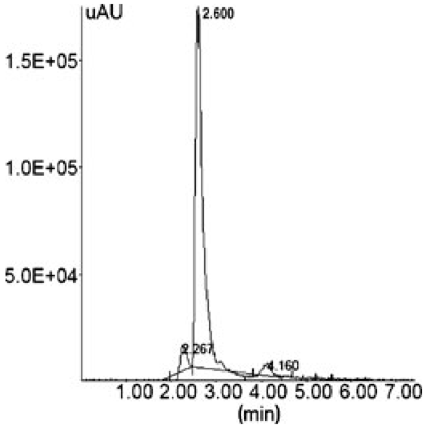


FIGURE 2 HPLC chromatogram for synthesized trimethylphosphite.

TABLE 1 The Yields of Synthesized Compounds

Compound	*x*	*R*	*R*^{1}	*Yield (%)*
1	0	–	CH_3	65
2	0	–	C_2H_5	72
3	0	–	*n*-C_3H_7	75
4	0	–	*n*-C_4H_9	69
5	0	–	$ClCH_2CH_2$	73
6	0	–	$C_6H_5CH_2$	74
7	1	CH_3	C_2H_5	77
8	1	C_2H_5	CH_3	69
9	1	C_2H_5	C_3H_7	68
10	1	C_2H_5	ClC_2H_4	79
11	2	C_2H_5	C_3H_7	80
12	2	C_2H_5	*i*-C_3H_7	69
13	2	C_2H_5	*n*-C_4H_9	81
14	2	C_2H_5	ClC_2H_4	73

hydroxide, led to formation of water when hydrochloric acid was neutralized. Potassium phosphate does not generate water in the neutralization process, so the side reactions were eliminated (Scheme 4).

EXPERIMENTAL

Materials

Phosphorus trichloride (Aldrich), methyldichlorophosphite (Aldrich), ethyldichlorophosphite (Aldrich), and diethylchlorophosphite (Aldrich), freshly distilled trimethylphosphite (Aldrich), methylene chloride (Aldrich), C_1–C_4 alkyl alcohols (Chemopar, Bucharest, Romania), benzyl alcohol (Aldrich), 2-chloroethanol (Aldrich), anhydrous potassium phosphate (Aldrich), and tetrahexylammonium chloride (Aldrich) were used.

Instruments

The ^{31}P-NMR spectra were recorded on a Bruker Avance DRX 400 at 400 MHz (85% H_3PO_4 was used as an external standard for ^{31}P and the solvent was $CDCl_3$; all spectra were recorded at room temperature). ABL&E JASCO HPLC was used to establish the purity of the products on C_{18} column with a UV detector (MD-1510). The yields were determined from distilled products.

$$Q^+Cl^- + K_3PO_4 \longrightarrow Q^+ {}^-PO_4K_2 + KCl$$

$$PCl_3 + 3\,ROH \longrightarrow (RO)_3P + HCl$$

$$HCl + Q^+ {}^-PO_4K_2 \longrightarrow Q^+Cl^- + K_2HPO_4$$

SCHEME 4 The proposed mechanism for synthesis of trialkyphosphites.

Synthesis of Trialkylphosphites from Phosphorus Trichloride (Compounds **1–6***)*

To a mixture of 0.03 mol K_3PO_4, 0.037 mol alcohol, and 0.001 mol tetrahexylammonium chloride as a catalyst in 10 mL methylene chloride, under stirring and external cooling (ice bath) 0.03 mol PCl_3 in 5 mL methylene chloride was added dropwise. The temperature was kept under 10°C during the addition of phosphorus trichloride, then the mixture was kept another 3 h at 20°C. The mixture was filtered; the solvent was removed by distillation, and the product wais purified by distillation (if required).

$(CH_3O)_3P$, liquid, bp 111°C/725 mmHg; $^{31}P\{^1H\}$, δ_P: 139.8 ppm (lit. [36,37]: 139.6–141 ppm). $(C_2H_5O)_3P$, liquid, bp 155°C/700 mmHG; $^{31}P\{^1H\}$, δ_P: 137.5 ppm (lit.[36,37]: 136.9–140 ppm). $(n\text{-}C_3H_7O)_3P$, liquid, bp 83°C/10 mmHg; $^{31}P\{^1H\}$, δ_P: 138 ppm (lit. [36,37]: 137.9 ppm). $(n\text{-}C_4H_9O)_3P$, liquid, bp 120°C/10 mmHg; $^{31}P\{^1H\}$, δ_P:138.9 ppm (lit. [36,37]: 137.7–142.6 ppm). $(ClC_2H_4O)_3P$, liquid, bp 114°C/3 mmHg; $^{31}P\{^1H\}$, δ_P: 139 ppm (lit. [36,37]: 138.7–139 ppm). $(C_6H_5CH_2O)_3P$, liquid, bp 150°C/0.1 mmHg; $^{31}P\{^1H\}$, δ_P: 140 ppm (lit. [36,37]: 138.8 ppm).

Synthesis of Mixed Trialkylphosphites from Methyldichlorophosphite or Ethyldichlorophosphite (Compounds **7–10***)*

To a mixture of 0.02 mol K_3PO_4, 0.025 mol alcohol, and 0.001 mol tetrahexylammonium chloride as a catalyst in 10 mL methylene chloride, under stirring and external cooling (ice bath) 0.02 mol methyldichlorophosphite or ethyldichlorophosphite in 5 mL methylene chloride was added dropwise. The temperature was kept under 10°C during the addition of phosphorus chloride, then the mixture was kept another 3 h at 20°C. The mixture was filtered; the solvent was removed by distillation, and the product was purified by distillation (if required).

$CH_3OP(OC_2H_5)_2$, liquid, bp 55°C/15 mmHg, $^{31}P\{^1H\}$, δ_P: 139 ppm. $C_2H_5OP(OCH_3)_2$: liquid, bp 30°C/14 mmHg; $^{31}P\{^1H\}$, δ_P: 139.2 ppm. $C_2H_5OP(C_3H_7)_2$, liquid, bp 75°C/12 mmHg, $^{31}P\{^1H\}$, δ_P: 138 ppm. $C_2H_5OP(OC_2H_4Cl)_2$, liquid, bp : 100°C/5 mmHg, $^{31}P\{^1H\}$, δ_P: 138.5 ppm.

Synthesis of Mixed Trialkylphosphites from Diethylchlorophosphite (Compounds **11–14***)*

To a mixture of 0.01 mol K_3PO_4, 0.015 mol alcohol, and 0.0005 mol tetrahexylammonium chloride as catalyst in 10 mL methylene chloride, under stirring and external cooling (ice bath) 0.01 mol diethylchlorophosphite in 5 mL methylene chloride was added dropwise. The temperature was kept under 10°C during the addition of diethylchlorophosphite, then the mixture was kept another 3 h at 20°C. The mixture was filtered; the solvent was removed by distillation, and the product was purified by distillation (if required).

$(C_3H_7O)P(OC_2H_5)_2$, liquid, bp 74°C/23 mmHg, $^{31}P\{^1H\}$, δ_P:138.5 ppm. $(i\text{-}C_3H_7O)P(O\ C_2H_5)_2$, liquid, bp 76°C/20 mmHg, $^{31}P\{^1H\}$, δ_P: 139 ppm (lit. [36]: 137.3 ppm). $(n\text{-}C_4H_9O)P(O\ C_2H_5)_2$, liquid, bp 72°C/10 mmHg, $^{31}P\{^1H\}$, δ_P: 139 ppm. $(C_2H_5O)_2P(OC_2H_4Cl)$, liquid, bp 115°C/5 mmHg, $^{31}P\{^1H\}$, δ_P: 137 ppm.

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